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Name: hyaluloran

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L9	L7 and cisplastin	0	L9
L8	L7 and therapy or prevention	291082	L8
L7	L5 and metastases	140	L7
L6	L5 and cytarabine	11	L6
L5	L4 and l2 and l1	172	L5
L4	hyaluronan	693	L4
L3	hyaluronan or hyaluronic acid	0	L3
L2	chemotherapy or antineoplastic agent	30439	L2
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L4	hyaluronan	693	L4
L3	hyaluronan orhyaluronic acid	0	L3
L2	chemotherapy or antineoplastic agent	30439	L2
L1	neoplasm or tumor	118842	L1

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L10: Entry 125 of 137 File: USPT Nov 2, 1999

DOCUMENT-IDENTIFIER: US 5977088 A
TITLE: Formulations containing hyaluronic acid

Brief Summary Text (2):
This invention relates to the treatment of disease and conditions of the skin and exposed tissue. In some embodiments this invention finds application to the treatment of a disease or condition of the skin and exposed tissue including basal cell carcinoma, squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies and tumours in the skin, genital warts (condyloma acuminata), cervical cancer, HPV (Human Papilloma Virus) including HPV (Human Papilloma Virus) on the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet, actinic keratoses lesions, "liver" spots, fungal lesions, and other such types of lesions, and hair loss on the head of a pregnant women.

Brief Summary Text (5):
Basal cell carcinoma is presently treated by surgery. Each lesion, together with all surrounding and underlying tissue (dermis, epidermis, and subdermis), is cut out. In some instances, surgery, while necessary for the patient's welfare, puts the patient at risk in some other respect (for example, the removal of a lesion on a patient's temple (resection) may jeopardize the patient's health). Squamous cell tumours are also treated the same way as are other forms of cancer in the skin and exposed tissue. Furthermore, other conditions and diseases of the skin and exposed tissue are treated in the same way or in ways that cause discomfort to the patient, for example melanoma, genital warts, cervical cancer, HPV (Human Papilloma Virus).

Brief Summary Text (23):
Applicants are also aware of published Japanese Patent Document 61000017, dated Jan. 6, 1986, whose English abstract of disclosure states that the Japanese Patent Document relates to the use of hyaluronic acid or cross-linked hyaluronic acid or their salts as the active ingredient for inhibiting carcinoma metastasis.

Brief Summary Text (30):
European Patent Application 0208623 purports to teach hyaluronic acid as "an augmentation of the activity of certain proteases". It also purports to teach the use of hyaluronic acid for treating connective tissue diseases, including malignant tumours and cardiovascular disorders.

Brief Summary Text (36):
There have been extensive studies to determine the defect in immune function that allows a tumour cell to develop. It was postulated, that the immune system's major role was that of immunological surveillance to destroy abnormal cells. The concept of surveillance, while somewhat simplistic, remains an accepted concept for the elaborate mechanism of immune recognition and function that is present in the higher species--mammals.

Brief Summary Text (37):
It has then been postulated that tumours develop because of local or generalized immune suppression. However, if general immune suppression occurs, it is only certain types of neoplastic disorders that develop, mainly those of the lympho-reticular system. This observation is generally correct and represents a major challenge to the immune surveillance theory unless a specific reason can be

shown as to why the individual cancer cell can develop plus individually evade the immune system.

Brief Summary Text (42):
It has recently been shown that the malfunction of macrophages or the putitive block is due to excessive prostaglandin and that this can be altered in tissue culture by corticosteroids, ASA, and the non-steroidal anti-inflammatory drugs, i.e. indomethacin and naproxen (Naprosyn.TM.). Again, it was repeatedly demonstrated that in animal tumours these substances could alter the response to neoplastic cells and that various combinations of these substances employed with immune enhancing agents could produce very credible success in eliminating experimental tumours. Researchers combined Indomethacin therapy with Interleukin 2 and showed that this could effect a cure with experiment neoplasm.

Brief Summary Text (43):
There were continued problems with the use of any of these agents in the actual human in vivo experience. All of the non-steroidal anti-inflammatory agents (NSAID) produced major toxicity in terms of gastro-intestinal, neurological, and other areas. Thus, the basis of the present approach is that, under general circumstances, with the use of these agents in human disease in sufficient amounts, the drug will penetrate to any pathological tissue to alter therapeutically local prostaglandin production. While intravenous preparations of Indomethacin (and now of other agents) exist, using these drugs alone produces prohibitive side effects in human subjects. Therefore, only insufficient amounts can be brought into the body to effect more than occasional responses in neoplasm.

Brief Summary Text (54):
Thus according to one aspect of the invention these pharmaceutical compositions (combinations and formulations) comprise a plurality of effective non-toxic dosage amounts for administration to the skin and/or exposed tissue of a human in need of treatment, each such dosage amount comprising a therapeutically effective non-toxic (to the patient) dosage amount of a drug to treat a disease and/or condition for example a drug which inhibits prostaglandin synthesis, preferably being a non-steroidal anti-inflammatory drug (NSAID), for example, diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac (sold under the trademark Toradol.TM.) and an effective non-toxic dosage amount (for example in excess of 5 mg per cm.sup.2 (square centimeter) of skin or exposed tissue to which the dosage amount of the composition is to be applied) of hyaluronic acid and/or salts thereof (for example the sodium salt) and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub units of hyaluronic acid (preferably hyaluronic acid and/or salts thereof) to transport (to faciliate or cause the transport of) the drug to the site of the pathology and/or trauma of the disease or condition. These compositions may be applied topically to treat diseases and conditions of the skin and/or exposed tissue at the site of the trauma and/or pathology, (for example, basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies and/or tumours in the skin, genital warts (condyloma acuminata), cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women). The results of the treatment with suitable dosage amounts taken from these compositions (combinations and formulations) have been in some instances quite dramatic--difficult situations have been successfully treated and resolved.

Brief Summary Text (57):
Thus, according to another aspect of the invention, Applicants have provided topically applicable percutaneous (intracutaneous) penetrating (best targeting the epidermis) systemic independent acting (not acting essentially through the blood) pharmaceutical compositions (combinations and formulations) comprising a plurality of dosage amounts each comprising, together with pharmaceutical excipients suitable for topical application, a therapeutically effective (to treat and to assist to resolve diseases and conditions of the skin and exposed tissue (for example basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis),

squamous cell tumours, metastatic cancer of the breast to the skin, malignancies and/or tumours in the skin primary and metastatic melanoma in the skin, genital warts (condyloma acuminata), cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women), non-toxic (to the patient) dosage amount of a drug for example which inhibits prostaglandin synthesis, preferably a non-steroidal anti-inflammatory drug (NSAID), for example, diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac (sold under the trademark Toradol.TM.) and an effective non-toxic amount of hyaluronic acid and/or salts thereof (for example, the sodium salt) and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid (preferably hyaluronic acid and salts thereof) to transport (facilitate or cause the transport of) the drug (for example NSAID's) rapidly to the site in the skin (for example epidermis) and/or exposed tissue of the disease or condition into the tissue to remain there for a prolonged period of time to assist to treat and assist to resolve the disease or condition for example by blocking prostaglandin synthesis.

Brief Summary Text (77):
Thus, according to another aspect of the invention, a method of treating a disease and/or condition of the skin or exposed tissue, for example basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies and/or tumours in the skin, genital warts (condyloma acuminata), cervical cancer, HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women, in a human is provided comprising administering topically to human skin and/or exposed tissue an effective non-toxic dosage amount of a composition comprising, together with pharmaceutical excipients suitable for topical application to the skin and/or exposed tissue, for example in the form of a gel or cream (to give the composition definition and form so that specific dosage amounts are easily selected or taken for administration (for example squeezed from a tube or scooped from a jar and rubbed into the skin or exposed tissue), a therapeutically effective (to treat and to assist to resolve the disease or condition for example basal cell carcinoma or other lesion), non-toxic (to the patient) dosage amount of a drug for example which inhibits prostaglandin synthesis, for example a non-steroidal anti-inflammatory drug (NSAID), for example, diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac (sold under the trademark Toradol.TM.) and an effective non-toxic dosage amount of hyaluronic acid and/or salts thereof (for example, the sodium salt) and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid (preferably hyaluronic acid and salts thereof) to transport (facilitate or cause the transport of) the drug (for example NSAID) into the skin or exposed tissue to the site of the disease or condition to be treated percutaneously, (to the site of trauma and/or pathology), for example into the epidermis, where the form of hyaluronic acid and medicine accumulates and remains for a prolonged period of time thereby for example blocking prostaglandin synthesis in the skin or exposed tissue. The form of hyaluronic acid is then cleared through the lymphatics (lymphatics system).

Brief Summary Text (85):
Delivery may be also accomplished by the same amount of the form of hyaluronic acid, of other drugs percutaneously (intercutaneously) to the skin and exposed tissue by application and rubbing in of an effective non-toxic dosage amount of the formulation or composition comprising an effective non-toxic dosage amount of the drug and an effective non-toxic dosage amount of the form of hyaluronic acid for the transport of the drug percutaneously into the skin or exposed tissue to the epidermis where the dosage amount of the composition is accumulated and remains for a prolonged period of time before the form of hyaluronic acid is cleared through the lymphatics. In this regard the drug may be novantrone (an anti-cancer drug) for administration to a tumour or malignancy in the skin. The novantrone may comprise 10 mg in the dosage amount of the composition and the form of hyaluronic acid may be in excess of about 5 mg of sodium hyaluronic per cm.sup.2 of the skin or exposed tissue (about 2.5% of the composition) for the percutaneous transport of the novantrone.

Brief Summary Text (90):
By way of example and to illustrate the facilitation of the delivery or transport of a chemical to a site in a human, when ethyl alcohol is injected directly into a tumour and sonographic (ultrasound) assessment is made, it is not dispersed throughout the tumour. When the ethyl alcohol to be administered into a tumour is carried by hyaluronic acid and/or salts thereof, sonographic assessment of the tumour demonstrates the dispersion of the ethyl alcohol throughout the tumour.

Brief Summary Text (95):
Thus, Applicants believe that the use of the NSAID, for example with hyaluronic acid (sodium hyaluronate), deblocks the macrophages (and N.K. cells (Natural Killer Cells) thought to be immature macrophages) by preventing enzymatic production of prostaglandin which blocks macrophage (and N.K. cell) functioning. The hyaluronic acid (and salt and other forms) not only enhances the activity of the drug (NSAID) but also reduces any side effects and toxicity that is associated with the use of the prostaglandin synthesis inhibitors. When effective dosage amounts of compositions, formulations and combinations containing effective dosage amounts of the drugs for example, (NSAIDs (for example, diclofenac)) and effective dosage amounts of, for example, hyaluronic acid or the sodium salt thereof, are applied to for example the tumour lesion (for example basal cell carcinoma) or other condition (for example, actinic keratoses lesion) for a period of time (for example, 3 times daily for 2-4 weeks), the carcinoma and lesions, as the case may be, disappear.

Brief Summary Text (100):
Thus according to another aspect of the invention, Applicants have provided compositions (formulations and combinations) (including pharmaceutical excipients suitable for topical application) from which effective non-toxic (to the patient) dosage amounts of a drug (for example an NSAID) to treat and to assist to resolve diseases and conditions of the skin and/or exposed tissue (for example basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies and/or tumours of the skin, gential warts, cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women), and effective non-toxic dosage amounts of hyaluronic acid and/or salts thereof (for example, the sodium salt) and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid (preferably hyaluronic acid and salts thereof) sufficient to transport (to facilitate or cause the transport of) the drug, for example NSAID, are taken for application, to a site in the skin (for example epidermis) or exposed tissue having a disease or condition for percutaneous transport into the skin and/or exposed tissue to accumulate and remain there for a prolonged period of time to for example block prostaglandin synthesis. Thus an effective dosage amount of the composition or formulation or combination penetrates quickly into the skin, for example by the hyaluronic acid transporting the NSAID or causing the NSAID to be transported for example to the epidermis of the skin, accumulates there and remains there for a prolonged period of time, thereby accumulating the drug and forms of hyaluronic acid in the skin (particularly the epidermis).

Brief Summary Text (101):
Thus according to another aspect of the invention, a method of accumulating a drug and a form of hyaluronic acid in skin and/or exposed tissue is provided comprising topically administering a therapeutically effective non-toxic dosage amount of a composition comprising pharmaceutical excipients suitable for topical applications, an effective non-toxic (to the patient) dosage amount of a drug for example which inhibits prostaglandin synthesis, preferably a non-steroidal anti-inflammatory drug (NSAID), for example, diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac (sold under the trademark Toradol.TM.) (to treat and to assist to resolve the disease and conditions of the skin and exposed tissue (for example basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous cell tumours, metastatic cancer of the breast to the skin, malignancies and/or tumours of the skin, primary and metastatic melanoma in the skin, genital

warts cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women), and an effective non-toxic dosage amount of hyaluronic acid and/or salts thereof (for example, the sodium salt) and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid (preferably hyaluronic acid and salts thereof) effective to transport (to facilitate or cause the transport of) the drug (for example NSAID) percutaneously to the site in the skin (for example epidermis) or exposed tissue of the disease or condition to accumulate and remain there for a prolonged period of time for example to block prostaglandin synthesis.

Brief Summary Text (102):
According to another aspect of the invention, a method of quickly delivering a drug to the skin or exposed tissue, particularly the epidermis, and maintaining the drug therein for a prolonged period of time is provided, the method comprising topically administering (for example rubbing in) an effective non-toxic dosage amount of a composition comprising pharmaceutical excipients suitable for topical application, a therapeutically effective (to treat and assist to resolve the disease and/or condition of the skin and exposed tissue (for example basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous cell tumours, metastatic cancer of the breast to the skin, primary and metastatic melanoma in the skin, malignancies and/or tumours of the skin, genital warts, cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women)), non-toxic (to the patient) dosage amount of a drug for example which inhibits prostaglandin synthesis, preferably a non-steroidal anti-inflammatory drug (NSAID), for example, diclofenac, indomethacin, naproxen, and (+/-) tromethamine salt of ketorolac (sold under the trademark Toradol.TM.) and an effective non-toxic dosage amount of hyaluronic acid and/or salts thereof (for example, the sodium salt) and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub-units of hyaluronic acid (preferably hyaluronic acid and salts thereof) sufficient to transport (to facilitate or cause the transport of) the drug for example the NSAID percutaneously to the site of the trauma and/or pathology in the skin (for example epidermis) or exposed tissue, for remaining there for a prolonged period of time (for example in the epidermis and dermis) to for example block prostaglandin synthesis. Suitable amounts of the form of hyaluronic acid may comprise in excess of 5 mg. per cm.sup.2 in a form which transports the drug (for example molecular weights of the form of hyaluronic acid being less than about 750,000 Daltons or if at substantially greater molecular weights, diluted (to reduce) the concentration or autoclaved or cleaved if required to reduce the size of the molecules.

Brief Summary Text (122):
One piece of skin (Female, 37 years, smoker, breast skin) was used for one sample from each batch. A second piece of skin (no further details available) was used for the second sample from each batch. The skin was stored deep frozen (<-20.degree. C.) until thawed for this experiment. Full thickness skin was used for this experiment.

Brief Summary Text (136):
FIG. 4 illustrates the results of the anti-cancer agent 5-fluoracil when administered alone and when administered with hyaluronic acid at varying times for tumor skin and normal skin, respectively.

Brief Summary Text (137):
FIG. 5 illustrates the radioactivity in tumor tissue.

Brief Summary Text (144):
FIGS. 12a and 12b show the response of p815 tumors in mice (strain DBA.sub.2) to treatment with novantrone and hyaluronic gel.

Detailed Description Text (5):
Further, the NSAIDs are retained in the area to be treated with the form of hyaluronic acid. In doing so, they preclude prostaglandin synthesis, in effect, deactivating the synthesis or inhibiting the synthesis, of prostaglandins,

permitting the macrophages' scavenger cell activity to eliminate the tumour and lesion. Additionally, a rapid onset of pain relief (analgesic effect) is provided (depending on the amount of NSAID and form of hyaluronic acid) usually where in excess of about 10 mg of the form of hyaluronic acid (preferably hyaluronic acid and salts thereof) is administered per cm.sup.2 of surface area comprises the dosage amount administered. However, there are no blood levels of the NSAID in the immediate area of treatment. The forms of hyaluronic acid are thus cleared via the lymphatic system. Then the lymphatics pass the forms of hyaluronic acid, Applicants believe, to the blood system. Thus, the NSAIDs and forms of hyaluronic acid stay at the site to be treated for well in excess of 12-24 hours, a protracted stay.

Detailed Description Text (6):
Thus, over the period of treatment (for example, applications of effective non-toxic dosage amounts of compositions containing for example effective non-toxic dosage amounts of the NSAIDS and effective non-toxic dosage amounts of the sodium hyaluronate, 3 times a day for 2-4 weeks, transport the NSAIDS to to the epidermis to inhibit prostaglandin synthesis to enable the macrophages to "scavenge" the tumour cells and eliminate them. The end result is the successful treatment of the disease or condition at the site of trauma and/or pathology of the skin or exposed tissue, for example, the resolution of, the basal cell carcinoma, the precancerous, often recurrent, actinic keratoses lesions, fungal lesions, "liver" spots and like lesions (found for the most part in the epidermis), squamous cell tumours, metastatic cancer of the breast to the skin, malignancies and/or tumours in the skin, primary and metastatic melanoma in the skin, genital warts cervical cancer, and HPV (Human Papilloma Virus) including HPV of the cervix, psoriasis (both plaque-type psoriasis and nail bed psoriasis), corns on the feet and hair loss on the head of pregnant women, with complete disappearance of the disease or condition as the case may be, by topical therapy without resorting to surgery.

Detailed Description Text (127):
Another form of sodium hyaluronate is sold under the name Hyaluronan HA-M5070 by Skymart Enterprises, Inc. having the following specifications:

Detailed Description Text (197):
A patient with dermal (skin) metastases in a fibratic scar form and metastatic cancer in the form of musculoskeletal involvement in her thorax.

Detailed Description Text (207):
Photographs were taken of patients with basal cell carcinoma FIGS. 6-11 photographs, and of mice with tumors induced in the skin of the hind legs (FIG. 12 photographs). The patients were treated by using combinations of NSAIDS, (non-steroidal anti-inflammatory drugs) and hyaluronic acid (including sodium hyaluronate) according to the invention (3% diclofenac in 2.5% sodium hyaluronate gel base). Each of the six sets of Figures made up of photographs of the different persons should include a legend describing or explaining each picture as follows:

Detailed Description Text (253):
Tumour: p815

Detailed Description Text (256):
The mice shown in FIGS. 12a and 12b had tumours induced in the skin of their hind legs and dosage amounts (2 ml) of Novatrone (10 mg. per dosage amount) (MITOXANTRONE (t.m.) and 2.5% sodium hyaluronate were applied (rubbed onto) the skin at the site of the pathology. The tumours reduced in size (See FIG. 12b) clearly illustrating the percutaneous delivery of the medicine by the hyaluronic acid. (See FIG. 12).

Detailed Description Text (264):
With respect to FIG. 12, (12a) shows mice having tumors in the skin induced in their hind legs. After continuous applications to the shaved hind legs having the tumors in the skin by rubbing in dosage amounts by Applicant's invention, the tumors have decreased in size. (See FIG. 12b)

Detailed Description Text (270):
b. Tumor model

Detailed Description Text (272):
Tumor (2 mm viable tumor fragment) was transplanted subcutaneously on the right frank by trocar

Detailed Description Text (273):
c. Treatment was started when tumor size is about 1.5 cm.

Detailed Description Text (279):
3H-FU without or with HA was injected as a single dose (0.3 ml) into the center of the tumor (on the right frank) with a 30 gause needle. At the same time, injection into normal skin (on the left frank) was carried out similarly.

Detailed Description Text (280):
The tumor and skin was then removed at different times (1 h, 6 hr) for counting radioactivity of the remaining content in the tissue.

Detailed Description Text (285):
1. In 5-FU HA group radioactivity was accumulated and retained in the tumor tissue for a long period, whereas rapid clearance was demonstrated in normal tissue. (skin)

Detailed Description Text (286):
2. In 5-FU group, radioactivity immediately disappeared from the tumor or the normal tissue by diffusion, primarily into blood capillaries.

Detailed Description Text (288):
The Effect of Hyaluronic Acid as a Drug Carrier in Target Cancer Chemotherapy

Detailed Description Text (292):
b. Tumor model

Detailed Description Text (294):
Tumor (2 mm viable tumor fragment) was transplanted subcutaneously on the right frank by trocar

Detailed Description Text (295):
c. Treatment was started when tumor size is about 1.5 cm.(2 weeks after implantation.) . . . tumor weight: 1.0+0.3 g

Detailed Description Text (301):
a. accumulation of ADR, 5-FU in tumor tissue and liver

Detailed Description Text (302):
(1). Tumor was surgically removed (and blood was collected) at *predeterminated time after drug administration. Tumor weight was measured (and blood was centrifuged to obtain a plasma sample.)

Detailed Description Text (305):
(2). Radioactivity level in tumor tissue was counted, using a liquid scintillation counter.

Detailed Description Text (307):
See FIG. 5 of Page 5/12 of the Figures which comprises a graph entitled "RADIOACTIVITY IN TUMOUR TISSUE" comparing CPM of the vertical with time in Minutes on the horizontal (for example 100, 200, 300).

Detailed Description Text (308):
1. Radioactivity in tumor tissue in 5-FU+HA group is higher than that in 5-FU group. There is significant difference (p>0.05, ANOVA) between with and without HA at 3 hrs after injection. The high intratumor concentration was retained for a prolonged time in 5-FU+HA group. (This retention was confirmed by the intratumor injection study.)

Detailed Description Text (309):
2. These results teach that HA can enhance 5-FU uptake in tumor tissue. This phenomenon results from HA distribution (in tumor tissue HA may be lost from the

extracellular matrix) and the vascular uniqueness of tumor tissue (hyperpermiability of tumor vessels to macromolecular drug, HA).

Detailed Description Paragraph Table (20):
TUMOR TISSUE NORMAL SKIN
(left hand portion (Right hand portion of the graph) of the graph) 1 STR1## 1 #STR2##

Detailed Description Paragraph Table (21):
Radioactivity in Tumor Tissue and Liver Tumor Liver 15 min 3H-5FU (n = 6) 2810 .+-. 165 18680 .+-. 625 3H-5FU + HA (n = 6) 352 .+-. 190 23593 .+-. 1460 3H-5FU + 3H-HA (n = 4) 4087 .+-. 681 32060 .+-. 2145 60 min 3H-5FU (n = 3) 1751 .+-. 149 5451 .+-. 841 3H-5FU + HA (n = 4) 2599 .+-. 489 8265 .+-. 1849 3 hrs 3H-5FU (n = 6) 1493 .+-. 227 2230 .+-. 449 3H-5FU + HA (n = 6) 2512 .+-. 449 2897 .+-. 340 3H-5FU + 3H-HA (n = 4) 3606 .+-. 929 6977 .+-. 1633 5 hrs 3H-FU (n = 3) 853 .+-. 129 1129 .+-. 70 3H-5FU + HA (n = 3) 1981 .+-. 479 1754 .+-. 248 3H-5FU + 3H-HA (n = 3) 2168 .+-. 163 3018 .+-. 325 mean .+-. S.E. HA: 15 mg/kg (30 .mu.Ci/kg) 5FU: 20 mg/kg (30 .mu.Ci/kg)

Other Reference Publication (3):
Adams JB. Steroid hormones and breast cancer. Dissertation Abstracts International 1981; 42(4): 1425B.

Other Reference Publication (58):
Di Cicco LM, Mansbridge JN, Morhenn VB. Inhibition of attachment and growth of tumor cells on collagen by a monoclonal antibody. In Vitro Cellular & Developmental Biology 1987; 23(12): 805-814.

Other Reference Publication (62):
Drobnik J. Hyaluronan in drug delivery. Advanced Drug Delivery Reviews 1991; 7: 295-308.

Other Reference Publication (113):
Kielty CM, Whittaker SP, Grant ME, Shuttleworth CA. Typ VI collagen microfibrils: Evidence for a structural association with hyaluronan. The Journal of Cell Biology 1992; 118(4): 979-990.

Other Reference Publication (125):
Larsen NE, Balazs EA. Drug delivery systems using hyaluronan and its derivatives Advanced Drug Delivery Reviews 1991; 7: 279-293.

Other Reference Publication (144):
Martin DE, Reece M, Reese AC. Effect of plasma fibronectin, macrophages, and glycosaminoglycans on tumor cell growth. Cancer Investigation 1984; 2(5): 339-345.

Other Reference Publication (168):
Nettelbladt O, Tengblad A, Hallgren R. High-dose corticosteroids during bleomycin-induced alveolitis in the rat do not suppress the accumulation of hyaluronan (hyaluronic acid) in lung tissue. Eur. Respir. J. 1980; 3: 421-428.

Other Reference Publication (221):
Stenfors L-E. Treatment of tympanic membrane perforations with hyaluronan in an open pilot study of unselected patients. Acta Otolaryngol (Stockh) 1987; Suppl. 442: 81-87.

Other Reference Publication (226):
Suzuki, Sakaru. (Dep't. of Chemistry, Faculty of Science, Nagoya University.). Symposium III Interaction between cell Stromata and Cancer: Interaction between Cells and Stromata in the Course of Cancer Cell Metastasis. [English Translation] Japanese Journal of Cancer and Chemotherapy 1984; 11(3): 557-780.

Other Reference Publication (240):
Turley EA, Austen K, Vandeligt, Clary C. Hyaluronan and a cell-associated Hyaluronan binding protein regulate the locomotion of Ras-transformed cells. The Journal of

Cell Biology 1991: 112(5): 1041-1047.

Other Reference Publication (259):
Zakut-Houri R, Oren M, Bienz B, Lavie V, Hazum S, Givol D. A single gene and a pseudogene for the cellular tumour antigen p53. Nature 1983; 306: 594-597.